In re Application of: Peled et al
Serial No.: 10/649,873
Filed: August 28, 2003
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Examiner: Bruce D. Hissong
Group Art Unit: 1646
Attorney Docket: 26732

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-76 are in this Application. Claims 1-52 and 56-76 have been withdrawn from consideration as being drawn to a non-elected subject matter. Claims 53-55 have been examined on the merits.

Claim 55 has now been canceled. Claims 53 and 54 have been amended. New claims 77-82 have been added.

Specification

The Examiner has noted that the trademarks used in the application should be capitalized wherever they appear and the accompanied by the generic terminology.

The specification has been amended accordingly, as follows:

Line 18 on page 19 and line 18 on page 32 have been amended so as to read: "...*TWEEN® 20 (polyoxyethylene (20) sorbitan monolaurate)*..."; and

Line 7 on page 22 and line 5 on page 35 have been amended so as to read: "... N*ikon DIAPHOT TMD Biological Inverted Microscope* ...".

While Applicant believes that Costar 3421 merely represents a catalog reference of a product by Corning, and is not a trademark, Applicant has chosen to amend line 19 on page 35 so as to read: "... *Costar 3421, Corning Costar, Cambridge, MA* ...".

Claim Objections

The Examiner has stated that claims 53-55 are objected to for depending from claim 10, which is drawn to non-elected subject matter.

Claim 53 has been amended so as to include the limitations of base claim 10, thereby overcoming the Examiner's objection.

As noted hereinbelow, Claim 53 has been further amended so as to include the limitations of claim 11, with respect to the claimed peptide.

New claims 77-81, reciting the limitations of claims 12-16 (dependent from claim 10) with respect to the claimed peptide, have been added. New claim 82, reciting some of the limitations previously recited in claim 13, has also been added.

35 U.S.C. § 112, first paragraph rejection (enablement)

The Examiner has rejected claims 53-55 under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for methods of treating diseases by administering a peptidic chemokine modulator other than SEQ ID NO: 64 (BKT-P45) and hence does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commesurate in scope with these claims. The Examiner's rejection is respectfully traversed. Claim 55 has been canceled. Claims 53 and 54 have been amended.

Specifically, the Examiner has stated that while the specification is enabling for a method of treating disease mediated by IL-8 by administering a therapeutically effective amount of the peptidic chemokine modulator BKT-45, it does not reasonably provide enablement for methods of treating disease by administering any other peptidic chemokine modulator. The Examiner has further stated that because many polypeptides can potentially comprise the recited amino acid residues, including two neighboring histidine residues, and have a positive charge, the breadth of the claims is excessive because the claims are drawn to methods of treating diseases by administering an unreasonably large number of potential peptides.

The Examiner has concluded that while the specification provides guidance and examples showing that the BKT-45 peptide inhibits IL-8-mediated cell adhesion and may thus be useful for treating diseases known in the art to be dependent upon IL-8-mediated chemotaxis, it does not provide guidance or examples showing that any other peptide/polypeptide is capable of inhibiting IL-8 or any other chemokine. The Examiner has continued stating that due to the unpredictability inherent in the art regarding which of the many potential peptides/polypeptides would be capable of

inhibiting any chemokine and thus be useful in the treatment of any chemokine-mediated disease, a person of ordinary skill in the art would require further, undue experimentation in order to make and use any peptide/polypeptide, other than BKT-45, for treating any disease other then those mediated by IL-8.

Applicant wishes to point out that the present invention is of selected peptides which were found capable of binding to chemokines and modulate their activity. These peptides were identified upon developing a process for screening a large number of peptides for potential chemokine binding, as detailed in the instant application (see for example, page 22, line 17 to page 24, line 17 therein) and is further delineated in a Declaration under 37 CFR 1.132 by Dr. Peled and Dr. Eizenberg, co-inventors of the present invention, which is submitted herewith.

Thus, a plurality of peptides were screened and only a fraction of these peptides were found to bind chemokines. The peptides identified as having chemokine binding capabilities were analyzed and some of these peptides were found to posses some common structural features. Peptides sharing common structural features were classified into two families, denoted as Family 1 and Family 2, based on these common structural features.

The fact that many of these peptides were found to have similar sequences is highly significant, and implies that these common features in the sequences of the peptides that bind chemokines are involved in the binding activity of the peptides. Moreover, because peptides that bind chemokines were found to exhibit modulation of chemokine activity (see, for example, page 26, line 7 to page 27, line 11 of the instant application and Table 4 therein), the common structural features of the peptide sequences can reasonably be assumed to be involved in the modulatory activity of these peptides.

Further evidence of the chemokine binding and inhibitory properties of Family 2 peptides is presented in the Declaration under 37 CFR 1.132 by Dr. Peled and Dr. Eizenberg, co-inventors of the present invention, submitted herewith.

Thus, as demonstrated in the Experimental Results presented in Appendix A of the Declaration, it has been found that each of the peptides of Family 2 bind to at least one of the chemokines IL-8, MIG and MCP-1.

In addition, IL-8, MCP-1 and MIG activity were each found to be inhibited by at least one of the Family 2 peptides tested (see, Table 2 in Appendix A of the Declaration).

In view of the above, it is clearly shown that (i) the binding of the chemokines IL-8, MIG and MCP-1 is a commonplace property of Family 2 peptides; and (ii) individual Family 2 peptides have been shown in general to inhibit the activity of chemokines to which they bind, and in particular to inhibit the activity of IL-8, MIG and MCP-1.

These data therefore provide clear evidence that the claimed Family 2 peptides bind to and inhibit the activity of at least the chemokines IL-8, MIG and MCP-1 and may thus be useful in the treatment of diseases known in the art to be dependent upon chemotaxis that is mediated by these chemokines.

Since the group of the claimed peptides was uncovered upon identifying peptides that are capable of binding to chemokines and further identifying the common structural features of these peptides, Applicant strongly believes that any person skilled in the art would recognize that peptides featuring these structural characteristics would exhibit the same binding and inhibition activities towards these chemokines and would be able to practice the invention without undue experimentation.

Notwithstanding the above, and in order to expedite prosecution, Applicant has chosen to amend claim 53 so as to read on peptides that are capable of inhibiting the activity of the chemokines IL-8, MIG and/or MCP-1.

Thus, claim 53 has been amended to recite:

"[a] method for treating a disease modulated through or caused by binding of a chemokine to a chemokine receptor in a subject, ***wherein said chemokine is selected from the group consisting of IL-8, MCP-1 and MIG****, ..." (emphasis added).*

Applicant therefore believes to have overcome the 35 U.S.C. § 112 first paragraph enablement rejection.

35 U.S.C. § 112 first paragraph rejection - written description

The Examiner has rejected claims 53-55 under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s) had possession of the claimed invention at the time the application was filed. The Examiner's rejection is respectfully traversed. Claim 55 has been canceled. Claims 53 and 54 have been amended.

In one particular, the Examiner has stated that the claimed peptidic modulators are not required to have any particular sequence or structure, but are only required to comprise the amino acids H, P, T, L, R, W and F, have at least two adjacent histidine residues, and have a positive charge, and that the claims do not require the peptidic chemokine modulators of the instant invention to have any biological activity other than to "modulate" any chemokine, and that the degree or type of modulation is not defined. The Examiner has further stated that the specification must provide sufficient distinguishing identifying characteristics of the genus, the factors to be considered including disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

As is well known in the art, the structural and chemical properties of peptides are characterized by the identity and sequence of the amino acids composing the peptide.

As argued hereinabove, regarding 35 U.S.C. § 112, first paragraph enablement rejection, the claimed peptides have been identified, out of a plurality of tested peptides, as capable of binding to chemokines and were grouped according to common structural features thereof. As further argued therein, the activity of these peptides in inhibiting the activity of certain chemokines, has been demonstrated in the instant application and is further supported by additional data presented in a Declaration under 37 CFR 1.132 by Dr. Peled and Dr. Eizenberg, submitted herewith.

Thus, the characteristics of the claimed peptides were determined in the course of the development of the present invention, as detailed hereinabove, by a process in which the chemokine binding capabilities of many peptides were investigated. The findings that peptides having similar structural characteristics also exhibit a similar activity toward binding to and inhibiting the activity of certain chemokines therefore clearly connect the chemokine modulation function of the claimed peptides to the structure and chemical properties of the claimed peptides.

It is therefore clear that at least the functional characteristics of the claimed peptides and the structure/function correlation thereof are specifically disclosed in the instant application and, furthermore, present distinguishing identifying characteristics of the claimed peptides.

Further, it is clear that the presence of two or more adjacent histidine residues, as specified by the claims, represents a partial structure of a peptide, particularly in short peptides of up to 20 amino acids, as specified in amended claim 53. In addition, the specification of a positive charge and the presence of the amino acids H, P, T, L, R, W and F, further indicate the chemical properties of the claimed peptides. As is well known in the art, the presence of a charge on the side chains of certain amino acid residues is a major determinant of the chemical properties of these amino acid residues, and of the chemical properties of the peptides comprising these residues.

Notwithstanding the above, and in order to more clearly define the functional characteristics of the claimed peptides, Applicant has chosen to amend claims 53 and

54, so as to recite inhibition as the type of modulation exhibited by the claimed peptides.

Thus claims 53 and 54 have been amended to recite "inhibit" instead of "modulate", "inhibitor" instead of "modulator", and "inhibition" instead of "modulation".

In addition, claims 53 and 54 have been amended, as mentioned hereinabove, to refer to the modulation of the chemokines IL-8, MIG and MCP-1, and therefore no longer refer to the modulation of any chemokine.

By way of clarification, claim 53 has been amended to recite *"... comprises at least two adjacent histidine residues and at least two amino acids selected from the group consisting of the amino acids P, T, L, R, W, and F"* in order to prevent any misunderstanding regarding the presence of the amino acids H, P, T, L, R, W and F in the definition of Family 2 peptides. Support for this amendment may be found for example, in Table 3 of the instant application, which demonstrates that Family 2 peptides all comprise at least two adjacent histidine residues and at least two amino acids selected from the group of P, T, L, R, W and F. Table 3 also includes a list of the frequency of amino acids in Family 2 peptides, demonstrating that H, P, T, L, R, W and F are the most abundant amino acids in Family 2 peptides.

In another particular, the Examiner has stated that the claims of the instant invention are drawn to treating genera of diseases that have not been adequately described in the specification.

Specifically, the Examiner has stated that the phrases "any type of malignant cell growth" and "acute and chronic bacterial and viral infections" in claim 55 do not adequately describe all possible types of malignant cell growth and bacterial and viral diseases that can be treated by inhibition of any chemokine, and that no common distinguishing factor(s) is disclosed among all possible types of malignant cell growth or bacterial and viral infections that would identify these genera.

Claim 55 has been canceled.

Applicant wishes to note, however, that diseases caused by binding of a chemokine to a chemokine receptor, wherein the chemokine is IL-8, mig and/or MCP-1 are well-recognized in the art and are recited in the instant application.

Applicant therefore believes to have overcome the 35 U.S.C. § 112, first paragraph, written description, rejections.

35 U.S.C. § 112, second paragraph rejections

The Examiner has rejected claims 53-55 under USC 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 55 has been canceled. Claims 53 and 54 have been amended.

In one particular, the Examiner has stated that claim 53, as well as dependent claims 54-55, is indefinite because of the use of "and/or", because it is not clear what controls which of these limitations.

Claim 53 has been amended so as recite "or" instead of "and/or".

In another particular, the Examiner has stated that the intended meaning of term "composed" in claim 10, from which claims 53-55 depend, is not clear.

Claim 53, from which claims 54 and 55 depend, has been amended such that it no longer depends from claim 10. Furthermore, claim 53 has been amended to recite:

"... **comprises** at least two adjacent histidine residues and at least two amino acids selected from the group consisting of the amino acids P, T, L, R, W, and F".

In yet another particular, the Examiner has stated that the metes and bounds of the terms "modulator", "modulation" and "modulates" are not defined by the claims or the specification, which do not define the type and degree of modulation, and thus the claims are indefinite.

As stated hereinabove, claims 53 and 54 have been amended to recite "inhibitor", "inhibition", and "inhibits" instead of "modulator", "modulation" and "modulates", respectively.

In still another particular, the Examiner has stated that claim 54 recites the limitation "the chemokines" with insufficient antecedent basis, and that claim 54 also recites "the chemokines" in the plural form, followed by a recitation of "the chemokine" in the singular form.

Claim 54 has been amended to recite (emphasis added):

"The method of claim 53 wherein said therapeutic agent binds to at least one **said chemokine** and wherein said therapeutic agent directly inhibits the activity of **said chemokine** by inhibition of binding of **said chemokine** to said chemokine receptor."

In yet another particular, the Examiner has stated that the phrase "non-optimal immune response", as recited in claim 55, is not an art-recognized disease, and that "non-optimal" is a relative term, and that the claim is therefore indefinite.

Claim 55 has been canceled.

Applicant therefore believes to have overcome the 35 U.S.C. § 112, second paragraph, rejections.

35 U.S.C. § 102(b) rejection - Eriksson et al.

The Examiner has rejected claims 53-55 under 35 U.S.C. § 102(b) as being anticipated by Eriksson et al. The Examiner's rejection is respectfully traversed. Claim 55 has been canceled. Claims 53 and 54 have been amended.

Specifically, the Examiner has stated that Eriksson et al. disclose a peptide that is comprised of the amino acids H, P, T, L, R, W and F, and has two neighboring histidine residues, and teach administration of the peptide for treating conditions characterized by reduced angiogenesis. The Examiner has further stated that it is known in the art that reduced angiogenesis is often a characteristic of diabetes, and therefore Eriksson et al. meet the limitations of claim 55 of the instant application.

The Examiner has further stated that the USPTO does not have the facilities for testing the overall charge of the peptide of Eriksson et al., and therefore the burden

is on the Applicant to show a novel and unobvious difference between the claimed peptidic chemokine modulator and the peptide of Eriksson et al.

The Examiner has still further stated that although Eriksson et al. does not teach that the peptide disclosed therein modulates the activity of any chemokine by modulation of binding to the chemokine receptor, in the absence of evidence to the contrary, it would be expected that the peptide of Eriksson et al. would have either a positive or a negative effect of some magnitude on the activity of a chemokine, and that because the USPTO does not have the facilities for testing the effects of the peptide of Eriksson et al. on chemokine activity or binding to any chemokine recetor, the burden is on the Applicant to show a novel and unobvious difference between the claimed peptidic chemokine modulators and the peptide of Eriksson et al.

As mentioned hereinabove, claim 53 has been amended to include the limitation: "a peptide up to about 20 amino acids in length". As demonstrated in the instant application, all the claimed peptides are no more than 20 amino acids in length.

Eriksson et al. teaches peptides considerably longer than 20 amino acids in length (see, for example, column 3, lines 49-65, claim 1, and SEQ ID NOs: 2, 3, 5, 7, 9, 11, 13 and 15 of Eriksson et al.).

As is well known in the art, short peptides, such as being of up to 20 amino acids in length, are highly advantageous, particularly in terms of therapeutic application, by being readily synthesized and purified, by being more stable and further by having improved biocompatibility and bioavailablity as compared to long peptides of 100 amino acids and more.

The use of such short peptides clearly presents a novel and unobvious difference between the claimed peptides and the peptides of Eriksson et al.

Applicant has therefore chosen, in order to more clearly distinct the claimed invention from the teachings of Eriksson et al., to amend claim 53, so as recite that the chemokine peptide inhibitor is up to 20 amino acids in length.

It is therefore the Applicant's opinion that amended claim 53, as well as amended claim 54 and new claims 77-82, which depend directly or indirectly therefrom, are not anticipated by Eriksson et al., and are therefore allowable.

35 U.S.C. § 102(e) rejection - Kovesdi et al.

The Examiner has rejected claims 53-55 under 35 U.S.C. § 102(e) as being anticipated by Kovesdi et al. The Examiner's rejection is respectfully traversed. Claim 55 has now been canceled. Claims 53 and 54 have now been amended.

Specifically, the Examiner has stated that Kovesdi et al. disclose a peptide that may comprise the amino acids H, P, T, L, R, W and F, and has two neighboring histidine residues and teach administration of the peptide for treating various diseases such as diabetes.

The Examiner has further stated that the USPTO does not have the facilities for testing the overall charge of the peptide of Kovesdi et al., and therefore the burden is on the applicant to show a novel and unobvious difference between the claimed peptidic chemokine modulator and the peptide of Kovesdi et al.

The Examiner has still further stated that although Kovesdi et al. does not teach that the peptide disclosed therein modulates the activity of any chemokine by modulation of binding to the chemokine receptor, in the absence of evidence to the contrary, it would be expected that the peptide of Kovesdi et al. would have either a positive or a negative effect of some magnitude on the activity of a chemokine, and that because the USPTO does not have the facilities for testing the effects of the peptide of Kovesdi et al. on chemokine activity or binding to any chemokine receptor, the burden is on the Applicant to show a novel and unobvious difference between the claimed peptidic chemokine modulators and the peptide of Kovesdi et al.

As mentioned hereinabove, claim 53 has been amended to include the limitation: "a peptide up to about 20 amino acids in length".

Although Kovesdi et al. teach a number of polypeptides comprising adjacent histidine residues, all such polypeptides taught by Kovesdi et al. are considerably more than 20 amino acids in length.

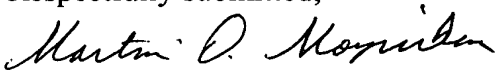
Furthermore, claim 53 has been amended, as described hereinabove, to specify IL-8, MCP-1 and MIG as the chemokines under the scope of the claim, and to specify inhibition as the type of modulation exhibited by the peptides of the instant claims.

Applicant does not believe that it would be expected that the peptide of Kovesdi et al., in the absence of any evidence, would have an inhibitory effect on the activity of one of the three abovementioned chemokines.

It is therefore the Applicant's opinion that amended claim 53, as well as amended claim 54 and new claims 77-82, which depend directly or indirectly therefrom, are not anticipated by Kovesdi et al., and are therefore allowable.

In view of the above amendments and remarks it is respectfully submitted that amended claims 53 and 54, as well as new claims 77-82, are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,



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Enclosures:

- Petition for Extension (3 Months)
- Additional Claims Transmittal Fee
- Declaration under 37 CFR 1.132 by Dr. Peled and Dr. Eisenberg, accompanied by the CVs Dr. Peled and Dr. Eisenberg